Appendix 3

Risk of bias in included studies

When assessing the quality of RCTs, bias is a very important consideration. We have looked at the various areas where bias may arise throughout the trials and given this an overall level of risk.

Selection

Allocation was randomised with Davidson et al using block randomisation, and with Omari et al, Orenstein et al and Wheatley et al using a random number generator. Corvaglia (b) et al and Corvaglia (a) et al did not report any form of random sequence generation for allocation. With regards to allocation concealment, Davidson et al is unclear about its methods of concealment.

Performance

Davidson et al, Omari et al, Orenstein et al and Wheatley et al all state or imply that their placebo was prepared and appeared similar to the drug, thus ensuring the blinding of participants and personnel. Corvaglia (b) et al and Corvaglia (a) et al were not clear about their methods taken to ensure blinding.

Detection

Data were assessed by independent assessors for Corvaglia (b) et al, Corvaglia (a) et al, Davidson et al and Wheatley et al minimising risk of detection bias. No apparent detection bias was found in Omari et al and Orenstein et al.

Attrition

Corvaglia (a) et al, Corvaglia (b) et al and Omari et al reported all outcomes. Davidson et al and Wheatley et al both lost 1 participant each to follow-up during the study; Davidson et al was due to efficacy data not being available, Wheatley et al does not give an explanation. 57 of 162 participants in Orenstein et al discontinued the treatment early giving a high risk of attrition bias. 55 of these participants went on to take open-label lansoprazole, the results of which were reported and incomplete data was carried forward to the 4^{th} week for the double-blind results. It is unclear what happened to the remaining 2 participants.

Risk of Bias Table – Corvaglia (b) et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear Risk	The DG ('drug-given') meal was randomly chosen in order to avoid any possible carry-over effect. As same study as Corvaglia (a) et al, it seems this was a random choice of data from 2 DG ('drug-given') and DF ('drug-free') feed in a 9 hour window.
Allocation concealment (selection bias)	Low Risk	Not relevant as all patients received treatment and placebo.
Blinding of participants and personnel (performance bias)	Unclear Risk	It is not clear whether the drug and placebo were very similar and if true blinding took place.
Blinding of outcome assessment (detection bias)	Low Risk	The investigator was blind to the administration of sodium alginate. pH-MII and PSG data were analysed independently by two different investigators.
Incomplete outcome data (attrition bias)	Low Risk	Outcome data appears complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	No conflicts of interest declared.

Risk of Bias Table - Corvaglia (a) et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear Risk	Each patient assessed over 24 hour period; 8 feeds with 2nd, 4th, 6th and 8th feed was DG ('drug-given') meal. No randomisation used.
Allocation concealment (selection bias)	Low Risk	Not relevant as all patients received treatment and placebo.
Blinding of participants and personnel (performance bias)	Unclear Risk	It is not clear whether the drug and placebo were very similar and if true blinding took place.
Blinding of outcome assessment (detection bias)	Low Risk	During layout analysis the investigator was blind to the administration of sodium alginate. pH-MII and PSG data were then analysed independently by two different investigators.
Incomplete outcome data (attrition bias)	Low Risk	Outcome data appears complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	No conflicts of interest declared.

Risk of Bias Table – Davidson et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	A block randomisation scheme was used, stratified by centre.
Allocation concealment (selection bias)	Unclear Risk	Method of randomisation allocation not clearly described.
Blinding of participants and personnel (performance bias)	Low Risk	Treatments blind to all, method described but not explicit that the active and placebo preparations looked identical.
Blinding of outcome assessment (detection bias)	Low Risk	Two blinded central readers independently reviewed the videos and cardiorespiratory data.
Incomplete outcome data (attrition bias)	Low Risk	One patient in the placebo group completed the study, but was lost to follow-up between study completion and the safety follow-up visit.
Selective reporting (reporting bias)	Low Risk	One patient in the esomeprazole group was excluded from the modified ITT analysis because of invalid efficacy measurements.
Other bias	High Risk	Sponsored by AstraZeneca LP (Wilmington, Delaware). AstraZeneca was involved in the design and conduct of the study; collection, analysis, and interpretation of the data; and the preparation, review, and approval of the trial report manuscript. 2 authors, both funded by AstraZeneca developed the first draft of the trial report manuscript. 3 employees of AstraZeneca, included work on this manuscript among their job responsibilities and also had limited AstraZeneca stock ownership. 3 authors had received grants and research support from AstraZeneca.

Risk of Bias Table – Omari et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	A stock solution containing either 5mg/mL omeprazole or sterile water was prepared and dispensed by pharmacy according to a randomisation schedule determined using a random number generator.
Allocation concealment (selection bias)	Low Risk	Drug or placebo prepared and dispensed using random number generator.
Blinding of participants and personnel (performance bias)	Low Risk	A stock solution was prepared which contained either omeprazole or sterile water (placebo). It is not clear how similar these were.
Blinding of outcome assessment (detection bias)	Low Risk	No apparent detection possible.
Incomplete outcome data (attrition bias)	Low Risk	Follow up data complete.
Selective reporting (reporting bias)	Low Risk	No apparent selective reporting.
Other bias	Low Risk	AstraZeneca R&D Molndal assisted by performing plasma omeprazole assays.

Risk of Bias Table – Orenstein et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Double-blind treatment assignments were made through a central web-based system according to a schedule that was computer generated.
Allocation concealment (selection bias)	Low Risk	States that treatment assignments were concealed to study personnel
Blinding of participants and personnel (performance bias)	Low Risk	Appearance, reconstitution, and administration of lansoprazole and placebo were identical.
Blinding of outcome assessment (detection bias)	Low Risk	No apparent bias in outcome assessment.
Incomplete outcome data (attrition bias)	High Risk	55 of 162 discontinued treatment early for open label treatment. For such subjects, the last week of available data was carried forward to 4th week for the individual symptoms and global severity assessments.
Selective reporting (reporting bias)	Low Risk	All randomised infants administered 1 or more dose(s) of study drug were included in the intention-to-treat data set for efficacy and safety analyses.
Other bias	High Risk	Takeda Global Research & Development Center, Inc sponsored the clinical trial, employed 2 authors and data interpretation and analysis was also undertaken by their employees.

Risk of Bias Table – Wheatley et al

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Low Risk	Study group assignment (order of medication and placebo administration) was determined by blocked random number generation.
Allocation concealment (selection bias)	Low Risk	A research pharmacist assigned the study group for each patient at the time of enrolment.
Blinding of participants and personnel (performance bias)	Low Risk	Investigators, clinicians, and parents were all blind to the group assignment during the study period. Intravenous preparations were used because they were clear and colourless. Saline placebos of the same volume and colour were administered during the placebo periods.
Blinding of outcome assessment (detection bias)	Low Risk	At the end of the study period for each infant, after the study outcome data were summarised for the infant, the investigator contacted the pharmacist to ascertain the group assignment (order of medication and placebo administration) for the infant, eliminating bias as data were analysed prior to finding out group assignment.
Incomplete outcome data (attrition bias)	Low Risk	One infant was enrolled in the study but was then withdrawn, with no explanation for the withdrawal.
Selective reporting (reporting bias)	High Risk	Clinicaltrials.gov record shows that the authors originally planned to analyse and present data on apnoea also. This was not included and the protocol was changed on clinicaltrials.gov.
Other bias	Low Risk	No conflicts of interest or sponsorship.